

# HEPARIN REDUCED MORTALITY AND SEPSIS IN SEVERELY BURNED CHILDREN

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**SUMMARY.** *Objectives.* In El Salvador, before 1999, morbidity and mortality in severely burned children were high. In 1998, all children with burns of 40% or larger size died and sepsis was found. With heparin use in 1999, some similarly burned children survived, and sepsis, pain, procedures, and scars were noted to be less. This retrospective study presents the details. *Methods.* A study was conducted at the National Children's Hospital in El Salvador of all children with burns over 20% size treated in 1998, when no heparin was used, and in 1999, when heparin was added to burns treatment, using an ethics committee approved protocol in use in twelve other countries. Sodium aqueous heparin solution USP from an intestinal source was infused intravenously and applied topically onto burn surfaces and within blisters for the first 1-3 days post-burn. Then heparin, in diminishing doses, was continued only topically until healing. The treatments in 1998 and 1999 were otherwise the same, except that fewer procedures were needed in 1999. *Results.* There were no significant differences in gender, age, weight, burn aetiology, or burn size between the burned children in 1998 and those in 1999. Burn pain was relieved and pain medicine was not needed in children treated with heparin in 1999. In 1998, one child survived who had a 35% size burn, and the eight children died who had burns of 40% and over. The survival rate was one out of nine (11%). The average burn size was 51.7%. With heparin use in 1999, six of the ten children survived burns of 50.7% average size. The increase in survival with heparin from 11% to 60% and, therefore, the decrease in mortality from 89% to 40% were significant ( $p < 0.04$ ). Clinical symptoms and positive blood cultures documented bacterial sepsis in the nine children in 1998. In 1999, the blood cultures for sepsis were positive in the four children who died and negative in the six who survived. The nine versus four differences in the incidence of sepsis between 1998 and 1999 was significant ( $p < 0.008$ ). The survivors had notably smooth skin. *Conclusions.* The use of heparin in this study relieved burn pain, significantly reduced mortality and sepsis with fewer procedures, and discernibly improved cosmetic results.

## Introduction

Starting in February 1999, following a presentation that reviewed the use of heparin in research studies in burned individuals,<sup>1</sup> the addition of heparin according to a protocol improved the treatment of burned children in El Salvador. Our initial findings<sup>2</sup> were similar to the results of burn researchers in 12 other countries, published in medical journals<sup>3,23</sup> or collected in the proceedings and syllabuses of international burn meetings, congresses, and symposia.<sup>24-31</sup> In these studies heparin was reported to inhibit blood clotting, relieve pain, reduce inflammation, restore blood flow, shorten healing time, and result in smooth skin. Infections, respiratory and intestinal tract complications, treatment procedures, and costs were reported to be less than those in prior cohorts of similarly burned patients who were treated without the use of heparin. The rationale for using heparin was strengthened by burn and non-burn studies that uncovered the mechanisms of heparin<sup>32-52</sup> (see Discussion). A search of the literature found no negative studies using heparin in burned humans.

In El Salvador, before 1999, morbidity and mortality in severely burned children were high.<sup>2</sup> In 1998, all chil-

dren with burns of 40% or more died and sepsis was found. With heparin use in 1999, some similarly burned children survived, and sepsis, pain, procedures, and scars were noted to be less. This study presents the method and results with heparin use in severely burned children in El Salvador in 1999 compared retrospectively with the results in 1998 in a similar cohort when *no* heparin was used.

## Method

*Subjects and location.* This study includes all paediatric patients with deep second- or mixed second- and third-degree burns of 20% or larger body size treated at the Benjamin Bloom National Children's Hospital in San Salvador, El Salvador, in 1998 and in 1999. The 300-bed hospital, with an average number of 16,000 admissions annually, is the principal national paediatric referral, treatment, and post-doctoral teaching centre for seriously ill or traumatized children, including burned children. The basic treatment of severely burned children was similar in 1998 and 1999 except for the use of heparin. No heparin was used in burn treatment in 1998. Heparin was added to the treatment in 1999, using a much-tested heparin therapy proto-

**Table I** - Survival in burned children treated without heparin in 1998, and with heparin therapy in 1999

											<u>Heparin Therapy</u>		
<u>Patients</u>					<u>Burn data</u>		<u>Hospital</u>	<u>Sepsis</u>	<u>Bleeding</u>	<u>Infusion</u>	<u>Topical</u>	<u>Total</u>	
	<u>Age</u>		<u>Weight</u>	<u>Survival</u>	<u>%</u>	<u>depth</u>	<u>Agent or</u>	<u>days</u>					
<u>Patient #</u>	<u>months</u>	<u>Sex</u>	<u>kg</u>	<u>status</u>	<u>surface</u>		<u>aetiology</u>				<u>Total IU</u>	<u>Total IU</u>	
											<u>IU / %s</u>	<u>IU / %s</u>	
											<u>IU / %s</u>	<u>IU / %s</u>	
<u>Children burned in 1998 - TREATED WITHOUT HEPARIN USE</u>													
1	71	F		Dead	20%	2nd deg	flame-fire		yes	no			
2	24	M	12	Dead	60%	2nd deg	boiling fluid	15	yes	no			
3	12	M	11.5	Dead	80%	2nd & 3rd	flame-fire	35	yes	no			
4	96	M	25	Alive	35%	2nd deg	flame-fire		yes	no			
5	51	M	15	Dead	80%	2nd deg	flame-fire	13	yes	no			
6	19	F	11	Dead	35%	2nd deg	boiling fluid	1	yes	no			
7	36	F	14	Dead	85%	2nd deg	boiling fluid	4	yes	no			
8	42	F	15.8	Dead	25%	2nd deg	boiling fluid	10	yes	no			
9	31	M	16	Dead	45%	2nd deg	boiling fluid	2	yes	no			
	total	382	4 F	1 survivor	51.7%	8 2nd deg		11.429	9 yes				
	average	42.444	5 M	8 deaths	35.0%	1 3rd deg			0 no				
					survivors								
					average								
	std deviation	+/- 26.801		+/- 4.470	+/- 0.252		std deviation	+/- 11.731					
<u>Children burned in 1999 - TREATED WITH HEPARIN USE</u>													
1	23	M	11	Dead	56%	2nd & 3rd	boiling fluid	7	yes	yes	17,000	66,000	
2	14	F	9	Dead	60%	2nd & 3rd	explosion fire	6	yes	no	35,000	45,000	
3	36	F	12.5	Dead	56%	2nd & 3rd	explosion fire	11	yes	no	20,000	800,000	
4	81	M	16	Alive	70%	2nd & 3rd	flame-fire	150	no	no	6,400	6,400	
5	55	M	20	Alive	60%	3rd deg	flame-fire	106	no	no	50,000	96,000	
6	5	F	7	Alive	20%	2nd deg	explosion fire	10	no	no	6,000	45,000	
7	96	F	25.5	Alive	45%	3rd deg	flame-fire	34	no	no	90,000	350,000	
8	12	M	9.4	Alive	50%	2nd deg	boiling fluid	14	no	no	8,000	10,000	
9	14	M	7.5	Alive	40%	3rd deg	boiling fluid	23	no	no			
10	3	M	6	Dead	50%	2nd & 3rd	flame-fire	5	yes	no	6,500	6,500	
	total	336	4 F	6 survivors	50.70%	2 2nd deg		36.600	4 yes		26,544	177,300	
	average	33.900	6 M	4 deaths	48%	8 3rd deg			6 no		32,080	101,480	
					survivors								
					average								
	std deviation	+/- 32.838		+/- 6.316	std deviation	+/- 0.137		std deviation	+/- 50.058				
Fisher's exact test = 0.617 0.9996 0.105 1.294													
df = 17 16 17 15													
p = 0.546 p = 0.605 0.332 p = 0.04 0.917 0.004 0.215 0.008													
Significance = ns ns ns significant ns significant ns significant													

col<sup>23</sup> approved by the Ethics Committee. *Table I* lists the age, sex, weight, survival status, burn size, severity, aetiology, days in hospital, septic status, and bleeding incidence of the children for the years 1998 and 1999. The burned children when first seen prior to treatment were typically in pain, crying, screaming, and struggling.

**Procedures.** In 1998 and 1999, burn size in the total body area and burn severity in depth were determined by clinical assessment. Determinations of histological depth were not performed. In 1998 and 1999, the same initial

routine burn treatment procedures were started: intravenous lines and infused fluids, vital signs, blood oxygen monitoring and administration, respiratory care, cardiac monitoring, urinary catheter placement, blood drawing for admission laboratory testing, pain medication administration, and tetanus toxoid inoculation. Bacterial cultures of infected burned skin areas were performed. Blood cultures were routinely performed to determine sepsis.

Demerol by injection was the medication used for pain. In 1998, Demerol was needed and routinely administered

in doses sufficient to control pain in all the children. In 1999, Demerol was only infrequently administered because burn pain was relieved with heparin use. The antibacterial cream applied topically and the water antimicrobial baths with debridement of necrotic tissue that were performed daily in 1998 were discontinued in 1999. The number of fasciotomies, escharotomies, and grafts performed in 1998 was higher than that performed in 1999, although the exact numbers are unknown.

In 1998, no heparin was used in the burned children. In 1999, heparin was administered parenterally and topically in all the burned children. No child had a contraindication to the use of heparin such as a personal or familial bleeding diathesis, a bleeding history, active bleeding or trauma with potential bleeding, an active peptic ulcer, a true allergy to heparin, or a thrombocytopenia. As a safeguard against bleeding, protamine sulphate was available: 1 mg of protamine neutralizes 100 IU of heparin. No protamine was used.

In 1999, sodium aqueous heparin solution (USP) from a swine intestinal source was administered in large doses both topically and intravenously on burn days 1 to 3, during the initial burn acidosis period. Then heparin was administered only topically, two or three times a day, in diminishing doses until final skin healing. The first intravenous heparin dose was a bolus infusion administered over a 3-5 min period. Then heparin was added to the intravenous fluids and administered in a continuous slow infusion. For scald-type burns, the total heparin intravenous day-one dose was usually 400 IU of heparin per kg body weight per 15% size burn. For explosion-, fire-, or smoke-type burns, a total day-one dose of heparin was usually a larger dose, in the 1000-1200 IU/kg per 15% burn size range.

The amount of heparin used was monitored by clinical signs: relief of pain and blanching of initial burn erythema, reduced swelling and oedema, decrease in burn size, drier burns, signs of revascularization, and progressive healing. Parenteral doses of heparin were also monitored by partial thromboplastin time blood clotting times, which were maintained in a clotting range that was one to three times longer than normal. Although the topical use of heparin was shown not to prolong systemic blood clotting times, the topical doses were monitored and regulated: revascularized granulation tissue received progressively less heparin, and burn areas with a tendency to bleed received no additional heparin. These heparin administration methods also functioned as techniques to avoid and prevent bleeding.

For topical use, in 1999, the 5,000 IU/ml dilution of heparin solution, contained in a 5- or 10-ml syringe with a number 30-gauge needle attached, was slowly and evenly dripped or sprayed onto the open burn surfaces of each burned child. The doctor or nurse did not initially touch the child. With the child held loosely by a relative, heparin solution was sprayed by the doctor or nurse from a distance of two or three feet through the needle and air

onto the painful burn surfaces, until all the burn surfaces had been treated once. Then burn blisters were treated. The syringe needle was introduced into each blister. A small opening was made in the blister so that the burn fluid would drain. Then heparin solution within the syringe was introduced inside the blister through the needle of the syringe. Slowly the blister was rinsed repeatedly with heparin solution, and finally a residual volume of heparin was retained within the blister space. Blisters were not removed. Burn surfaces were then retreated at 5-10 min intervals for 20-30 min. The few blisters that later partially refilled with burn fluid were again rinsed out with the heparin solution a second or third time either the same or the next day. Topical treatment of burn surfaces was continued two or three times a day, using rapidly reducing amounts of heparin, until final healing. *Table I* lists the quantity of heparin administered to each child, intravenously and topically, and the total amount.

The study data for 1998 and 1999 (*Table I*) were statistically analysed.

Student tests (t-tests) and Fisher exact tests were used to evaluate the differences between the 1998 and the 1999 data. An alpha level of 0.05 or less was accepted as statistically significant.

## Results

As shown in *Table I*, there were no significant differences in age (average 42 versus 34 months), weight (average 15 versus 12.4 kg), or sex in the nine children with severe burns of 20% or more in 1998 compared with the ten children with burns of similar size in 1999. The 51.7% average burn size in 1998 was essentially the same as the 50.7% average burn size in 1999, and not statistically different. Two children were designated as having appreciable third-degree burns in 1998 compared with eight children with appreciable third-degree burns in 1999. Although the children treated with heparin were noted to be more severely burned than those not receiving heparin therapy ( $p < 0.004$ ), there was statistically greater mortality in the non-heparin treated group ( $p < 0.04$ ). The number of burned children found to have sepsis in 1998 was also significantly greater ( $p < 0.008$ ). In 1998, the one child survived who had a 35% total body surface area (TBSA) burn, and the other eight children, who had larger size burns, all died. The survival rate in 1998 was one out of nine (11%) and the mortality rate eight out of nine (89%). In 1999, using heparin, the survival rate increased to six out of ten (60%) and the burn mortality rate dropped to four out of ten (40%). One of the ten heparin-treated children in 1999 had appreciable bleeding on a burn surface. Bleeding may to some extent have contributed to the death of this particular 23-month-old child, who had boiling fluid burns in 56% TBSA, but sepsis was clinically surmised to have been a major contributor to death, as the blood cultures were positive.

In 1998, without heparin, pain medicine was needed to relieve pain in all the burned children. In 1999, using heparin, no pain medicine was needed. The pain in every heparin-treated burn surface quickly subsided, usually within a minute. The children stopped crying, screaming, and struggling, becoming co-operative, and soon permitted a doctor or nurse to treat their painful blisters, which relieved the pain there. Intravenous use of heparin promptly relieved deep burn pain. The noisy din and distressing emotional ambience of the emergency room or the burn ward soon gave way to a quiet calm. Continued use of heparin consistently relieved recurrent surface or deep pain.

The blisters, which were treated with heparin and were not debrided, did not become infected, as a rule, and they required no further care. Collapsed blisters functioned as skin grafts. In time, new smooth epithelium was evident when the thin dry blister remnant flaked away, within 2-3 weeks.

Other beneficial results using heparin in 1999 are noteworthy. They were similar to results in studies reported by burn researchers in the United States, India, Russia, Bulgaria, Brazil, Mexico, Haiti, Oman, China, South Korea, Malaysia, and Nepal.<sup>1,7-22,24-31</sup> Burn and body swelling was minimal. Also, the amount of resuscitation fluid used did not appreciably contribute to swelling. Hence, fewer surgical incisions, escharotomies and fasciotomies were needed or performed. Routine use of skin grafts ceased in 1999. A few smaller size skin grafts were applied in 1999 to hasten healing and reduce hospital time. Revascularization was enhanced and accelerated. The new skin in the six survivors in 1999 was smooth.

Compared with 1998, burn care in 1999 was simplified. Routine daily baths using water with an antimicrobial agent became unnecessary and were discontinued. Topical antibiotic creams were not used for research results, and they were found to be unnecessary. The procedures used to prevent bleeding were effective. Only one transfusion of blood was used, in the child with surface bleeding. It is not known if the bleeding contributed to the patient's death. No other complications were noted in the children who survived.

## Discussion

The use of large doses of both intravenous and topical heparin in burned children in El Salvador in 1999 clearly improved the treatment of burned paediatric patients compared with 1998, when heparin was not used. The 1999 component of this study was an Ethics Committee approved study in burned children of the effects of heparin used according to a standardized protocol. Although the group comparisons of heparin versus no heparin were conducted retrospectively, no systematic bias emanated from the 1998 data, since the benefits of heparin burn therapy were unknown at that time to the doctors who treated the burned children. Also, in 1998 and 1999, the burned children were treated in the same setting by the same doctors,

the addition of heparin in 1999 being the principal test variable.

In 1999, with the use of heparin, more children (six out of ten) and younger children (34 months old on average) survived than in 1998 (one out of nine, and 42 months old), when burn treatment was without heparin therapy. The increase in survival with heparin therapy in 1999 has additional importance because the burns in 1998 were significantly less severe as regards depth, i.e. two out of nine in 1998 presented third-degree burns involvement versus eight out of ten in 1999 ( $p < 0.004$ ). The significant decrease in the incidence of sepsis in 1999 (using heparin) versus 1998 (without heparin) ( $p = 0.008$ ) was consistent with the mortality finding. Previous studies are supportive of this sepsis outcome. One study found a significant preservation of intestinal lining and a significant decrease in translocation of bacteria through the intestinal wall when heparin was used in the treatment of third-degree burns of 25 and 35% surface size in mice.<sup>48</sup> Another study<sup>24</sup> found that the use of heparin decreased sepsis.

Several burn studies using heparin have reported alterations in mortality rates. A 1951 study<sup>1[8].5</sup> found that untreated control dogs with 50% third-degree burns died in 34.6 hours on average, while dogs infused with anticoagulating doses of heparin survived 72.2 hours on average. When the study was repeated in 1974<sup>9</sup> survival was prolonged beyond the 120 h duration of the experiment when larger doses of heparin were given. Survival in sheep subjected to fatal inhalations of smoke was prolonged from 60 to 96 h with increased doses of heparin administered parenterally<sup>45,46</sup> or by inhalation.<sup>46</sup> There was an improvement in lung function and a decrease in mortality in burned children with lung involvement who were treated with inhalations of heparin or n-acetylcysteine alternately every 2 h.<sup>47</sup>

Mechanisms illuminating the modes of action of heparin have been revealed in burn and non-burn studies. Heparin reversibly inactivated known mediators of inflammation at acidic pHs.<sup>1[10-13,29,32-39].34</sup> It promoted neoangiogenesis by stimulating the migration of endothelial cells into ischaemic tissue, where they multiplied to form new capillaries that restored blood flow.<sup>1[43,44,51].42-44</sup> Heparin regulated collagen activity in granulation tissue, initially accelerating and then decelerating production.<sup>1,15,21,52</sup> Heparin influenced the proliferation of dermal fibroblasts and the aligning of their intracytoplasmic fibrils into a regular parallel pattern that resulted in smooth skin.<sup>1[52,54].49,50</sup> In scars, without the use of heparin, the distribution pattern was a chaotic clumping beneath the cell membrane. Parenteral or inhalation use of heparin preserved pulmonary tissue, improved lung function, and increased survival.<sup>45-47</sup> Heparin also preserved intestinal mucosa and reduced bacterial translocation from the intestinal tract.<sup>48</sup> Also, heparin administered in intravenous infusions is the medicine of choice and the accepted therapy for blood stasis, thromboses, emboli, and disseminated intravascular coagulopathy found in burn pathology.

## Conclusions

In severely burned children with comparable large burns of similar average size, the addition of heparin therapy resulted in a significant 49% decrease in mortality ( $p < 0.04$ ) and a significant reduction in sepsis ( $p < 0.008$ ). The relief of burn pain, the enhanced healing, and the

smooth skin previously reported using this therapy were similarly evident in the present study. These findings and the appreciable, but not quantified, reduction in procedures and costs to more sustainable and affordable levels may be of interest to doctors who treat burns in other countries, especially those with limited current technological and financial resources.

**RÉSUMÉ.** *Buts.* Au Salvador, avant 1999, la morbidité et la mortalité chez les enfants atteints de brûlures sévères étaient élevées. En 1998, tous les enfants atteints de brûlures en 40% de la surface corporelle ou de plus sont décédés et un état septique a été observé. En 1999, avec l'emploi de l'héparine, d'autres enfants atteints de brûlures comparables ont survécu, et le sepsis, la douleur, les procédures et les cicatrices étaient mineurs. Cette étude rétrospective présente les détails. *Méthodes.* Les Auteurs ont effectué l'étude au National Children's Hospital (Salvador), considérant tous les enfants atteints de brûlures dans au moins 20% du corps traités en 1998, sans l'emploi d'héparine, et en 1999, quand l'héparine a été ajoutée au traitement des brûlures, suivant un protocole approuvé par un comité éthique utilisé en douze autres pays. La solution aqueuse d'héparine aqueuse de sodium USP de source intestinale a été infusée par voie intraveineuse et appliquée topiquement sur les surfaces des brûlures dans les premiers 1-3 jours après la brûlure. Ensuite l'héparine a été administrée seulement topiquement, en dosages toujours mineurs, jusqu'à la guérison. A part cela, les traitements en 1998 et 1999 étaient identiques, sauf que le numéro de procédures en 1999 était mineur. *Résultats.* Les enfants brûlés observés en 1998 ne présentaient aucune différence significative de sexe, âge, poids ou étiologie et extension de la brûlure par rapport aux enfants de l'année successive. La douleur causée par les brûlures a été allégée et aucune médecine de la douleur n'a été nécessaire chez les enfants traités avec l'héparine en 1999. En 1998, un seul enfant atteint de brûlures de 35% a survécu, tandis que les huit enfants atteints de 40% ou de plus de brûlures sont morts. Le taux de survie a été donc d'un enfant sur neuf (11%). L'extension moyenne des brûlures était de 51,7%. En 1999, avec l'emploi de l'héparine, six des dix enfants ont survécu à des brûlures d'une extension moyenne de 50,7%. L'augmentation de la survie avec l'héparine de 11% à 60% et, conséquemment, la réduction de la mortalité de 89% à 40% ont été significatives ( $p < 0,04$ ). En 1998, les symptômes cliniques et les cultures sanguines positives ont documenté un sepsis bactérien chez tous les neuf enfants. En 1999, les cultures sanguines pour le sepsis ont été positives chez les quatre enfants décédés et négatives chez les six enfants survivus. Cette différence de neuf contre quatre dans le taux de sepsis entre les deux années 1998 et 1999 était significative ( $p < 0,008$ ). La peau des patients survivus était notablement lisse. *Conclusions.* Les Auteurs concluent que dans cette étude l'emploi de l'héparine a diminué la douleur due aux brûlures, réduit en manière significative la mortalité et le sepsis, avec un numéro inférieur de procédures, et amélioré visiblement les résultats cosmétiques.

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